Targeting Remission in Moderate-to-Severe Crohn's Disease

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Inflammatory bowel diseases, such as ulcerative colitis (UC) and Crohn's disease (CD), are chronic conditions that can severely impact a person's quality of life and lead to serious complications. UC affects only the mucosal lining within the colon, whereas CD may involve any part of the gastrointestinal (GI) tract from the mouth to the anus; it most commonly affects the ileum.[1] An estimated 780,000 Americans are diagnosed with CD and, when combined with UC, these diseases are thought to account for $11 billion to $28 billion in annual health care costs.[1,2]

The pathophysiology of CD involves the interaction of multiple factors, including patient genetics, the microflora inhabiting the GI tract, and environmental exposures. This multifactorial etiology may help explain the disparity in patient responses to available therapies and the challenges in identifying appropriate therapies. Regardless of origin, the end result is an inflammatory response in the lining of the GI tract resulting in damage and compromised function. Initial manifestations can vary depending upon the disease location and severity of inflammation, but typical symptoms include abdominal pain, fatigue, weight loss, and diarrhea with or without blood. Over time, more serious complications can develop, including fistulas, strictures, abscesses, perforation of the bowel, or nutritional deficiencies from malabsorption. Patients with CD may also develop extraintestinal complications, including kidney stones, arthritis, or iritis.[3] Complications from the disease may ultimately necessitate surgical intervention. In a sample of patients with severe disease (n = 321) observed for 15 years, intestinal resection was needed in 59% of patients, and 14% required the placement of a permanent stoma.[4]

Patients are generally categorized as having low- or moderate/high-risk disease based on symptoms and presentation.[5] The treatment goal for every patient is to achieve disease remission, demonstrate healing of the mucosal lining, and reduce the frequency of serious complications and need for surgery.[6] A common tool for classifying patients is the Crohn's Disease Activity Index (CDAI) in which a score less than 150 indicates remission and a score greater than 450 indicates severe disease.

Patients with mild disease are usually managed with local anti-inflammatory therapies or systemic corticosteroids, and patients with moderate-to-severe disease require more aggressive treatment with immunosuppressants or targeted biologic therapies. This article focuses on moderate-to-severe CD. The Food and Drug Administration (FDA)-approved agents for this indication are provided in Table 1.

Several areas in which the treatment of CD needs development are:

- Improving the efficacy and safety seen with current therapies, particularly in patients who fail to respond to anti-tumor necrosis factor (TNF) agents.
- Identifying biomarkers for better prediction of patient response.
- Identifying therapies to treat perianal fistulas.
- Improving patient adherence to chronic treatment through simpler regimens, better education, and increased medication tolerability.[7]

Many companies are developing novel agents; however, these therapies are not always effective. Recently, Celgene discontinued two phase 3 trials for its novel Smad7 inhibitor mongersen.[8] Although the drug demonstrated some positive outcomes in phase 2 trials, it failed to show benefit during an interim futility analysis of larger studies.[7,8] The failure of this agent illustrates how the identification of biomarkers does not always translate into viable targets. This review presents several upcoming therapies in phase 3 development that are poised to enter the global market in the coming years.

Etrolizumab

Etrolizumab, in development by Genentech, is a monoclonal antibody targeting the subunits α4β7 and αEβ7 on the integrin receptor. Blocking this receptor inhibits the movement of leukocytes into the gut and may reduce chronic inflammation. The targeting of αEβ7 distinguishes etrolizumab from Entyvio (vedolizumab, Takeda), which only inhibits α4β7—but it remains to be seen whether this additional blockade leads to improved patient response.[7]

There are limited data regarding the clinical effects of etrolizumab in CD patients because the completed phase 2 trials only evaluated patients with UC. Although the potential efficacy in CD patients is unknown, adverse effects in UC patients occurred in 48% to 61% of etrolizumab-treated patients versus 72% of patients receiving placebo, demonstrating the general tolerability of the agent. The most common adverse effects reported included disease flares of UC, headache, and nervous system disorders.[9]

Two phase 3 trials are currently evaluating the efficacy and safety of etrolizumab in CD patients. BERGAMOT, a 14-week induction trial, aims to enroll 1,150 patients with moderate-to-severe CD, regardless of anti-TNF status. The dosing regimens being evaluated are subcutaneous (SQ) injections containing 105 mg or 210 mg of etrolizumab every four weeks versus placebo. The results from BERGAMOT are expected by June 2019.[10] Patients who achieve remission can subsequently be enrolled in the open-label extension study, JUNIPER. This trial will aim to follow 900 patients receiving 105 mg of etrolizumab via SQ injection for up to 6.5 years after initial enrollment. The anticipated completion date is May 2024.[11] The positioning of etrolizumab will be determined by its ability to demonstrate improved efficacy compared with other integrin-targeting therapies; a SQ injection formulation of Entyvio is also under development.[7]

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Table 1 Current FDA-Approved Medications for Moderate-to-Severe Crohn's Disease[27]

Generic Name *Brand, Manufacturer*	Mechanism Of Action	Formulations	General Maintenance Dosing	Estimated AWP (per dose)*	Generic?
Azathioprine	Inhibition of purine synthesis and DNA replication	Oral tablet	2–3 mg/kg daily	$17	Yes
Methotrexate	Folate antimetabolite that inhibits DNA synthesis and repair	IM or SQ injection	15–25 mg weekly	$162	Yes
Infliximab *Remicade, Janssen Biotech*	Anti-TNF-alpha	IV infusion	5 mg/kg every 8 weeks	$4,903	Biosimilar approved
Adalimumab *Humira, AbbVie*	Anti-TNF-alpha	SQ injection	40 mg every 2 weeks	$2,923	Biosimilar approved
Certolizumab *Cimzia, UCB*	Anti-TNF-alpha	SQ injection	400 mg monthly	$8,088	None
Vedolizumab *Entyvio, Takeda*	Inhibition of α4β7 integrin	IV infusion	300 mg every 8 weeks	$5,863	None
Ustekinumab *Stelara, Janssen Biotech*	Inhibition of IL-2 and IL-23	SQ injection	90 mg every 8 weeks	$20,584	None
Natalizumab *Tysabri, Biogen*	Inhibition of α4β1 and α4β7 integrin subunits	IV infusion	300 mg every 4 weeks	$6,180	None

* Price calculated for 70-kg patient.

AWP = average wholesale price; IL = interleukin; IM = intramuscular; IV = intravenous; SQ = subcutaneous; TNF = tumor necrosis factor.

Filgotinib

The team of Galapagos and Gilead is looking to enter multiple markets with the selective Janus kinase 1 (JAK1) inhibitor, filgotinib. In addition to the treatment of CD, this medication is also being evaluated in patients with rheumatoid arthritis. JAK1 is an intracellular protein kinase responsible for a number of cellular processes, such as proliferation and differentiation; dysfunction in this signaling pathway has been linked to many diseases, including CD.[7]

Results from the phase 2 FITZROY study of filgotinib have been published. This trial randomized 174 patients with moderate-to-severe CD to receive 200 mg of filgotinib daily versus placebo for 10 weeks. The primary endpoint was disease remission, defined as a CDAI score less than 150. At week 10, 47% (60 of 128) of treated patients achieved remission compared with 23% (10 of 44) of placebo patients. Differences in response to filgotinib were also noticed based on a patient's history of exposure to anti-TNF therapies. TNF-naïve patients had a greater response to filgotinib than patients who were TNF experienced, with clinical response rates of 60% (34 of 57) versus 37% (26 of 71), respectively.

The rates of treatment-emergent adverse effects were similar between filgotinib and placebo at 75% versus 67%, respectively. Serious adverse events resulting in discontinuation were seen in 18% of filgotinib patients compared with 9% of placebo patients.[12] The difference in patient response based on anti-TNF status may indicate that filgotinib is not a viable option for patients who are refractory to anti-TNF therapies.[13]

A phase 3 trial, DIVERSITY, will evaluate filgotinib for induction and maintenance therapy in 1,320 patients with moderate-to-severe CD with an anticipated completion date late in 2019.[14] An extension trial (DIVERSITYLTE) will continue to follow the same patients for up to 144 weeks to evaluate long-term safety.[15] Other trials are also under way in specific CD populations, such as those with perianal fistulizing disease or small-bowel CD.[16,17] Safety data from these ongoing trials will be significant in determining filgotinib's place in clinical practice; it should be noted that tofacitinib (Xeljanz, Pfizer), a nonselective JAK inhibitor, is associated with potentially serious adverse effects, such as increased infections and the development of malignancies.[18]

Risankizumab

Now that some biosimilar agents are competing with AbbVie's adalimumab (Humira), the company is looking to expand its CD profile with risankizumab. Positioned as a direct competitor to Janssen's interleukin (IL)-23 inhibitor ustekinumab (Stelara), risankizumab is a humanized monoclonal antibody that targets the p19 subunit of IL-23, which subsequently inhibits the binding of IL-23R and activation of the proinflammatory JAK/STAT intracellular signaling pathway.[7]

The results of a phase 2 trial in which 121 patients received induction therapy with intravenous (IV) risankizumab 200 mg or 600 mg, or placebo every four weeks, with assessment of response at week 12, were published in 2017.[19] Of those enrolled, 93% had prior anti-TNF therapy exposure. Achievement of remission (CDAI less than 150) was seen in 24%, 37%, and 15% of patients receiving risankizumab 200 mg, risankizumab 600 mg, and placebo, respectively. Documentation of endoscopic remission, defined as a 50% improvement in bowel lining seen via endoscopy, was observed in 15% and 20% of patients receiving 200 mg and 600 mg of risankizumab,

Table 2 Therapies in Late-Stage Development for Crohn's Disease[7]

Medication *Developer*	Mechanism Of Action	Targeted Indication/ Population	Route and Dose	Expected Price Strategy	Anticipated Launch Date
Etrolizumab *Genentech*	Inhibition of α4β7 and αEβ7 integrin subunits	Maintenance therapy for patients with moderate-to-severe CD who are naïve, refractory, or intolerant of TNF-alpha antagonists	SQ injection Induction dosing: 210 mg initially and at weeks 2, 4, 8, and 12 Maintenance dosing: 105 mg every 4 weeks	Anticipated pricing at 5% premium to IV vedolizumab (Entyvio, Takeda)	2021
Filgotinib *Galapagos/ Gilead*	JAK1 inhibitor	Patients with moderate-to-severe CD who are TNF-alpha-naïve or -experienced May also have role in perianal fistulizing disease and small-bowel disease	Once-daily oral tablet 100–200 mg daily for 10 weeks for CD (24 weeks for fistulizing/ small-bowel disease)	Anticipated at 10% discount to annual cost of tofacitinib (Xeljanz, Pfizer) Pricing may depend on how filgotinib is priced in RA market	2021
Risankizumab *AbbVie*	IL-23 inhibitor	Patients with moderate-to-severe active CD who are refractory to TNF-alpha antagonists	IV infusion and SQ injection Dosing not finalized	Anticipated pricing at 5% premium to ustekinumab (Stelara, Janssen Biotech)	2021
SHP-647 *Shire*	Monoclonal antibody targeting MAdCAM-1	Patients with moderate-to-severe CD who are refractory to TNF-alpha antagonists	SQ injection Doses of 22.5 mg, 75 mg, and 225 mg every 4 weeks have been evaluated	Anticipated pricing at 5% premium to IV vedolizumab	2021

CD = Crohn's disease; IL = interleukin; IV = intravenous; JAK1 = Janus kinase 1; MAdCAM-1 = mucosal addressin cell adhesion molecule-1; RA = rheumatoid arthritis; SQ = subcutaneous; TNF = tumor necrosis factor.

respectively, compared with 3% of placebo patients. Rates of adverse effects were similar in all three groups, with the most commonly observed events being nausea, abdominal pain, and worsening of CD.[19]

The FDA has already approved risankizumab as an orphan drug for the treatment of pediatric CD, and phase 3 trials are underway in adults. A double-blind, placebo-controlled trial enrolling 940 patients with moderate-to-severe CD will be evaluating endoscopic and clinical response in patients receiving undisclosed doses of SQ or IV risankizumab for 12 weeks.[20] A smaller trial targeting patients who have failed prior biologic therapies is under way with an estimated completion date in 2019. This trial will explore differing induction doses as well as routes of administration compared with placebo.[21] Patients responding to induction in either of the previous trials can further be enrolled in a 52-week, double-blind, placebo-controlled extension that will evaluate risankizumab as a maintenance therapy and compare the SQ versus IV routes.[22]

The positioning of risankizumab will depend on its performance in phase 3 studies and its efficacy and safety compared with ustekinumab. If the selective properties of risankizumab can demonstrate an advantage and if the pricing is competitive, risankizumab has the potential to be a first-line biologic therapy.

SHP-647

Shire is in the process of developing SHP-647 after having acquired the license from Pfizer. This agent is an antihuman monoclonal antibody targeting mucosal addressin cell adhesion molecule-1 (MAdCAM-1). As an extracellular protein, SHP-647 is important in the adhesion and movement of leukocytes into the GI tract. Blocking this pathway may allow for targeted reduction of inflammation in the GI tract while not impairing leukocyte migration to other organs.[7]

The phase 2 OPERA trial enrolled 265 patients who had failed or could not tolerate anti-TNF therapy or immunosuppressants to receive placebo or SQ injections of 22.5 mg, 75 mg, or 225 mg of SHP-647 every four weeks. The primary endpoint, a 70-point decrease in CDAI score, was seen in 58.6% of placebo patients and in 62%, 64.7%, and 57.5% of patients receiving 22.5 mg, 75 mg, and 225 mg of SHP-647, respectively. CDAI remission at week 12 was seen in 23% of placebo patients compared with 26.8%, 28.5%, and 29.6% of patients receiving 22.5 mg, 75 mg, and 225 mg of SHP-647. These findings were disappointing given the similar outcomes in the placebo arm; however, investigators did notice differences in several laboratory endpoints. Significant reductions in concentrations of soluble MAdCAM (88% to 97% with treatment versus 6.7% with placebo) were observed along with an increase in circulating B_7 central CD4+ memory cells. It was also noted that patients receiving treatment had a 20% to 31% reduction in circulating C-reactive protein while placebo patients had a 5.6% increase.[23]

OPERA II was a 72-week, phase 2 extension study that evaluated the safety and efficacy of SHP-647 in patients with moderate-to-severe CD. Patients were able

to receive a range of doses from 22.5 mg to 225 mg (with a starting dose of 75 mg) SQ every four weeks based upon the need for increased disease control and the severity of adverse effects. Of the 268 enrolled patients, 149 completed the study. The most common reasons for discontinuation were withdrawal by study participant, insufficient clinical response, adverse effects (unrelated to study drug), and loss to follow-up. The commonly reported adverse effects were generally mild (i.e., nasopharyngitis [5.6%], arthralgia [6%], headache [5.2%]), but 80 patients experienced severe adverse effects, with 10 being described as drug-related. The most common adverse effect leading to drug discontinuation was disease flare of CD.[24,25] A phase 3, long-term safety extension trial of patients with both UC and CD is in the process of recruitment and has a projected completion date of 2025.[26]

Given the negative clinical findings of the OPERA study, the positioning of SHP-647 in the treatment of CD may be difficult without either establishing a biomarker that identifies the population most likely to benefit or strong results from phase 3 trials.[7]

CONCLUSION

Dozens of other medications are in various stages of development for the treatment of CD. These future therapeutic options include both small-molecule entities and targeted monoclonal antibodies, thereby offering a broad range of approaches to this complex disease. The addition of new biosimilar agents to the existing options of infliximab and adalimumab, the current standards of care, will change clinicians' approach to treating CD if the new agents allow for improved access to treatment and lower health care costs.

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